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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,741	11/14/2005	Hiroyuki Aburatani	392.1001	4248

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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddk@ddkpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/526,741	ABURATANI ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9, 23-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9, 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed March 24, 2008 in response to the Office Action of November 21, 2007 is acknowledged and has been entered. Previously pending claims 9 and 27 have been amended. Claims 9 and 23-29 are currently being examined.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 9 and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lage et al. (Virchows Arch 2001 438:567-573, IDS), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al.(Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53).

Lage et al. teach the production of a monoclonal antibody to GPC3 using an oligopeptide of amino acids 537-556 of human GPC3, see Materials and Methods. Lage et al. use the standard art technique of fusing spleen cells from immunized mice with myeloma cells to generate hybridomas for the production of the monoclonal antibody, which leads to recombination of the fused cellular genomes, thus the monoclonal antibodies are recombinant antibodies. Lage et al. teach that the glycosyl-phosphatidylinositol anchor GPC3 protein is expressed in hepatocellular carcinomas, decreasing in expression in tumor grade, see Abstract, table 1, Fig. 2-4.

Lage et al. does not teach that the antibody has any cytotoxic activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells or a humanized form of the antibody.

Steplewski et al. teach that mouse monoclonal antibodies are humanized to overcome the problem of short half-life and immunogenicity of murine monoclonal antibodies in humans, see page 4852, first paragraph. Steplewski et al. teach the generation of humanized mouse monoclonal anti-bodies using Cγ1, Cγ2, Cγ3, and Cγ4 human heavy chains and human Cκ light chains, see Materials and Methods. Steplewski et al. that these humanized antibodies can

mediate antibody dependent cell mediated cytotoxicity, ADCC, *in vitro* in the presence of peripheral blood monocytes, see Abstract, Materials and Methods, and Fig.4.

Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity, see p. 593, 1st col.

Mast et al. teach that GPC3 is expressed on the surface of HepG2 cells, see Title, Abstract, and Introduction.

Midorikawa et al. teach that GPC3 protein is found in elevated levels in HepG2 cells and 22 of 52 hepatocellular carcinomas examined.

It would be *prime facia* obvious to one of skill in the art at the time the invention was made to humanize the monoclonal antibody of Lage et al. using the methods of Steplewski et al. to make humanized monoclonal antibodies that have Cγ1, Cγ2, Cγ3, or Cγ4 human heavy chains and human Cκ light chains that have cytotoxic activity in the presence of complement or peripheral blood mononuclear cell as Steplewski et al. teach that humanization of antibodies is done to overcome the problems of using mouse monoclonal antibodies in human therapy. Additional Steplewski et al. teach that these humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes and Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity. One would have been motivated to humanize antibodies the monoclonal antibody of Lage et al. to screen them for potential therapeutic antibodies using HepG2 cells that expressed GPC3 on their surface given that Lage et al. and Midorikawa et al. teach that GPC3 is expressed in hepatocelllular carcinomas, given that HepG2 cells express GPC3 on their cell surface at elevated levels, and given the importance of developing new cancer

therapeutics. One of skill in the art would have had a reasonable expectation of success of making a humanized, monoclonal antibody against a peptide consisting of amino acid residues 375-580 of GPC/SEQ ID NO: 4 that has cytotoxic activity in vitro against HepG2 cells in the presence of mononuclear cells or complement given that the monoclonal antibody of Lage et al. binds within amino acid residues 375-580 of GPC3, the methods for humanizing antibodies were well known in the art at the time the invention was made, and the humanized antibodies claimed were known to have to cytotoxic activity in the presence of complement or peripheral blood mononuclear cells.

3. Claims 9 and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Filmus et al. (US Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53).

Filmus et al. teach the production of a monoclonal antibody to GPC3 using the last 70 amino acids of human GPC3, see para 0098 and 0107-0109 and claims 7 and 33. Filmus et al. use the standard art technique of fusing spleen cells from immunized mice with myeloma cells to generate hybridomas for the production of the monoclonal antibody, which leads to recombination of the fused cellular genomes, thus the monoclonal antibodies are recombinant antibodies, see para 0098 and 0107-0109. Filmus et al. teach that the monoclonal antibody 1G12 bound strongly to human liver tumor cells, but not normal hepatocytes, see Examples 4 and 5.

Filmus et al does not teach that the antibody has any cytotoxic activity *in vitro* against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells or a humanized form of the antibody.

Steplewski et al. teach that mouse monoclonal antibodies are humanized to overcome the problem of short half-life and immunogenicity of murine monoclonal antibodies in humans, see page 4852, first paragraph. Steplewski et al. teach the generation of humanized mouse monoclonal anti-bodies using Cγ1, Cγ2, Cγ3, and Cγ4 human heavy chains and human Cκ light chains, see Materials and Methods. Steplewski et al. that these humanized antibodies can mediate antibody dependent cell mediated cytotoxicity, ADCC, *in vitro* in the presence of peripheral blood monocytes, see Abstract, Materials and Methods, and Fig.4.

Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity, see p. 593, 1st col.

Mast et al. teach that GPC3 is expressed on the surface of HepG2 cells, see Title, Abstract, and Introduction.

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It would be *prime facia* obvious to one of skill in the art at the time the invention was made to humanize the monoclonal antibody of Filmus et al using the methods of Steplewski et al. to make humanized monoclonal antibodies that have Cγ1, Cγ2, Cγ3, or Cγ4 human heavy chains and human Cκ light chains that have cytotoxic activity in the presence of complement or peripheral blood mononuclear cell as Steplewski et al. teach that humanization of antibodies is done to overcome the problems of using mouse monoclonal antibodies in human therapy.

Additional Steplewski et al. teach that these humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes and Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity. One would have been motivated to humanize antibodies the monoclonal antibody of Filmus et al to screen them for potential therapeutic antibodies using HepG2 cells that expressed GPC3 on their surface at elevated levels given that Filmus et al. and Midorikawa et al. teach that GPC3 is expressed in hepatocelllular carcinomas and given the importance of developing new cancer therapeutics. One of skill in the art would have had a reasonable expectation of success of making a humanized, monoclonal antibody against a peptide consisting of amino acid residues 375-580 of GPC/SEQ ID NO: 4 that has cytotoxic activity in vitro against HepG2 cells in the presence of mononuclear cells or complement given that the monoclonal antibody of Filmus et al binds within amino acid residues 375-580 of GPC3, the methods for humanizing antibodies were well known in the art at the time the invention was made, and the humanized antibodies claimed were known to have to cytotoxic activity in the presence of complement or peripheral blood mononuclear cells.

4. All other objections and rejections recited in November 21, 2007are withdrawn.

5. No claims allowed.

6. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

7. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/

Examiner, Art Unit 1642

/P. J. R./

/Karen A Canella/

Primary Examiner, Art Unit 1643